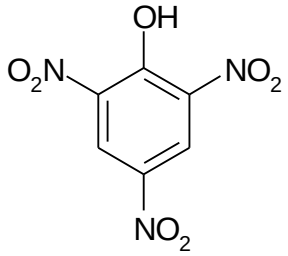
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	88-89-1
Chemical Name	Picric acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical properties

Picric acid is a pale yellow, odourless, intensely bitter crystal with relatively high water solubility of 11.8 g/L at 20 °C (measured). Picric acid has an explosive property when shocked or heated, especially reactive with metals or metallic salts. Melting point is 122.5 °C and explodes above 300 °C. Vapour pressure is 5.1×10^{-5} Pa at 25 °C (estimated), and partition coefficient between octanol and water (Log K_{ow}) is 0.89 at pH1.0 (measured). Dissociation constant of pK_a = 0.16 at 20 °C (measured) indicates that picric acid exists primarily as an anion in aquatic compartment or moist soil surfaces.

Human Health

Picric acid was administered to male rats by intravenous injection (50 mg/kg bw) or by oral gavage [100 mg/kg bw]. At 24 h after intravenous injection, 81.5% of administered radioactivity was cleared from the blood with 58.9% excreted in the urine and 12.2% in the faeces. The plasma half-life was 13.4 h. After oral administration, approximately 60% of the dose was absorbed within 24 h. The highest concentration of radioactivity was detected, in a decreasing order, in the spleen, kidney, liver, lung, and testes. In the urine collected over a 24-period, approximately 60% of total radioactivity was unchanged parent compound. Major urinary metabolites were N-acetylisopicramic acid (14.8%), picramic acid (18.5%) and N-acetylpicramic acid (4.7%).

The oral LD_{50} values were 492 mg/kg bw for male rats and 283 mg/kg bw for female rats (OECD TG 401). Observed clinical signs included decrease in locomotor activity, abnormal gait, clonic convulsions and loose stool, which were also found in surviving animals at 400 mg/kg bw. In dead animals, pathological changes such as haemorrhage, hard wall and thickening of the wall were observed in the glandular stomach. In another study (not according to OECD guideline), the oral LD_{50} values were 290 mg/kg bw for male and 200 mg/kg bw for female rats. Tremors, violent tonic/clonic convulsions, circumorbital discharge (chromodacryorrhea) of the eye, and a fall in blood pH were observed. No reliable information was available regarding acute toxicity via dermal and inhalation routes.

Although no reliable information on skin irritation was available, it has been reported that picric acid in the form of a crystalline solid as well as aqueous solution can produce skin irritation. As for eye irritation, there is one reliable study, in which rabbits showed minimal irritation to the solid form of picric acid and the recovery within 24 h. Other available information on eye irritation was not reliable, but provided the following: a solution of picric acid was reported to be injurious to rabbit eyes although the details were not available.

Picric acid was positive for skin sensitization in a split adjuvant test in guinea pigs. In humans, only secondary literature reported sensitization dermatitis in munitions workers. This suggests the possibility that picric acid can cause skin sensitization in human.

A 28-day guideline study of the repeated dose toxicity of picric acid was performed. The compound was

administered via gavage to 6 or 12 rats/sex/dose at 0, 4, 20, or 100 mg/kg bw/day 7 days/week for 4 weeks. No deaths were observed in either sex. At the highest dose tested, the absolute and relative spleen weight and the relative liver weight were increased in both sexes. In males of the 100 mg/kg bw group, decrease in the absolute and relative weight of the epididymis was also found. Histopathological and haematological examinations revealed haemolytic anemia, as evidenced by reductions in red blood cells and haemoglobin, and haemosiderin deposition and extramedullary haematopoiesis in the spleen in both sexes in 100 mg/kg bw dose group. Furthermore, altered development of germinal centres in the spleen, ulcers of the cecum and centrilobular hypertrophy of hepatocytes were found in both sexes in the 100 mg/kg bw dose group. Based on these effects, the NOAEL for 28-day repeated dose oral toxicity in male and female rats was considered to be 20 mg/kg bw/day.

In a reproduction/developmental toxicity screening test, rats (12 animals/sex/dose) were administered picric acid by oral gavage at a dose of 0, 4, 20, or 45 mg/kg bw/day (OECD TG 421). The compound was administered to males for 46 days from day 14 before mating to the day before sacrifice and to females from day 14 before mating and throughout mating and pregnancy to day 3 of lactation. No deaths occurred. Reduced body weight gain was noticed among males in the 45 mg/kg bw dose group. Increases in the relative weights of the liver and kidneys and a decrease in the absolute weight of the epididymis in males as well as increases in the absolute and relative weights of the liver and spleen in females were observed at this dosage. Based on these results, the NOAEL for repeated dose oral toxicity was considered to be 20 mg/kg bw/day.

In a bacterial reverse mutation assay (Ames test) conducted according to the OECD TG 471, picric acid was shown to be positive in *Salmonella typhimurium* TA 98 and TA1537 without metabolic activation and in *Salmonella typhimurium* TA100, TA1535, TA98 and TA1537 with metabolic activation. Positive results were also observed in some strains in other bacterial reverse mutation assays. An *in vitro* chromosomal aberration test (OECD TG 473) using cultured Chinese hamster lung cells was positive only at cytotoxic doses (1600 and 1800 μg/mL) without metabolic activation. In a chromosomal aberration test using Chinese hamster ovary cells, negative results were obtained up to 1000 μg/mL without metabolic activation. Both of these chromosomal aberration tests showed negative results under the presence of metabolic activation. Picric acid dose-dependently induced sister chromatid exchange in Chinese hamster ovary cells under the absence of metabolic activation. In a mouse micronucleus test, male and female mice (2 animals/sex/dose) were administered picric acid twice (0 and 24 h) at doses of 0, 22.9, 68.7, or 91.6 mg/kg bw (intraperitoneal injection) or 0, 229, 343, or 458 mg/kg bw (per oral). Micronucleated polychromatic erythrocytes did not increase at any dose. In Drosophila SLRL mutation tests, positive results were obtained after injection of picric acid, but feeding studies provided conflicting results. In the reciprocal translocation test with *Drosophila* sp. by injection, the substance showed negative results. Based on these results, picric acid is considered to be genotoxic *in vitro*. Although no induction of micronucleus was observed in mammals, it is not possible to exclude genotoxicity, as the potential for picric acid to cause gene mutations has not been investigated *in vivo*.

No data were available on the carcinogenicity of picric acid.

In the above-mentioned reproduction/developmental toxicity screening test (OECD TG 421), picric acid was administered via gavage to 12 animals/sex/dose at 0, 4, 20 or 45 mg/kg bw/day, for 7 days/week for 46 days in males and from day 14 before mating, throughout the mating and pregnancy periods, to day 3 of lactation in females. Reproductive performances were not affected in parental animals. At necropsy, the absolute weight of the epididymis was decreased among males in the 45 mg/kg bw dose group. In the testes, retention of step-19 spermatid in stage IX-XI was found in two males at 45 mg/kg bw/day. Quantitative analysis of spermatogenesis revealed a decrease in the number of pachytene spermatocytes in stage I-VI at 45 mg/kg bw/day. There was also a slight atrophy of seminiferous tubules in one male each at 20 and 45 mg/kg bw/day. However, such small incidences of atrophic changes with weak severity are occasionally observed in control rats, and also these pathological changes may be justified as an independent phenomenon from the stage (I-VI) specific spermatogenesis effect at the dose of 45 mg/kg bw/day; therefore, these slight atrophy of seminiferous tubules were considered not to be an adverse effect. The NOAEL for this study was considered to be 20 mg/kg bw/day in rats.

The above-mentioned 28-day repeated oral dose toxicity study using rats clearly demonstrated the male reproductive toxicity of picric acid at the higher doses. Organ weight measurements revealed decreases in the absolute and relative weights of the epididymides in the 100 mg/kg bw dose group. Histopathological examination revealed diffuse atrophy of the seminiferous tubules of the testes (6/6 males), cell debris in the lumen (4/6 males) and decrease in the number of sperms in the epididymis (6/6 males) in the 100 mg/kg bw group. These changes were also observed after a 14-day withdrawal period. There were no changes in the weight and histopathology of male reproductive systems in the 4 and 20 mg/kg bw groups. These results suggested that reproductive performances would be affected at the dose of 100 mg/kg bw/day. Based on the

above studies, the NOAEL for reproductive toxicity was considered to be 20 mg/kg bw/day.

As for the developmental toxicity, there have not been any formal investigations (e.g. prenatal developmental toxicity study); however, in the above-mentioned reproductive and developmental toxicity screening test (OECD TG 421), no adverse effects on development were observed up to the highest dose tested. In another study, picric acid was administered by gavage to newborn rats at doses of 0, 4.1, 16.3, or 65.1 mg/kg bw/day from postnatal days 4 to 21 (for a total of 18 days). Lower body weight and higher relative liver weight were observed at a dose of 65.1 mg/kg bw, but the animals exhibited no abnormal changes in developmental landmarks, reflex ontogeny, urinalysis, or sexual maturation at all doses. Based on these results, the NOAEL for developmental toxicity in rats was considered to be 45 mg/kg bw/day.

Picric acid may present a hazard to human health (skin and eye irritation, skin sensitization, acute oral toxicity, repeated dose toxicity, reproductive toxicity and genotoxicity). Adequate screening level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

In the atmosphere, picric acid is expected to be degraded by hydroxyl radicals. A calculated half-life time of 75.914 days and a rate constant of 0.14×10^{-12} cm^3/molecule-sec were obtained by AOPWIN for the indirect photo-oxidation by reaction with hydroxyl radicals in air.

Picric acid is not hydrolysed due to the lack of hydrolysable functional groups. A hydrolysis test according to OECD Test-guideline 111 showed that picric acid was stable in water at pH 4, pH 7 and pH 9 at 50 °C for five days.

A test result of picric acid with activated sludge showed 23% degradation by BOD after a 28 day cultivation period according to OECD test guideline 301C. BIOWIN estimation predicts that picric acid is not ready biodegradable. According to these results, picric acid is considered to be not-readily biodegradable.

In a study performed according to the equivalent protocol with OECD test-guideline 305C with carp over a 6 week exposure period at concentrations of 0.5 mg/L or 0.05 mg/L, bio-concentration factors were less than 0.24 for the 0.5 mg/L treatment and less than 2.2 for the 0.05 mg/L treatment. Taking into account the octanol-water partition coefficient, a bio-concentration factor can be calculated as 3.16 according to a log K_{ow} of 0.89 by BCFBAFWIN. These results show a low potential for bioaccumulation of picric acid for aquatic organisms. As picric acid has log K_{oc} of 2.0 (estimated with log K_{ow} of 0.89) and exists as an anion in moist soil, mobility in the soil is expected to be high.

As picric acid is present in dissociated form in the environment mainly in the water phase; the distribution using the fugacity model is difficult to be estimated accurately. Based on its low pK_a value, the substance is expected to be present in the environment in the anionic form. As anions are neither subject to volatilisation nor to adsorption, the hydrosphere is the target compartment for this chemical.

The following acute toxicity test results have been determined for aquatic species:

Fish [*Onchorynchus mykiss*]:	96 h LC50 = 110 mg/L (nominal)
Daphnid [*Daphnia magna*]:	24 h $L(E)C_{50}$= 85and 145 mg/L (nominal)
	48 h $L(E)C_{50}$= 85, 86 and 90 mg/L (nominal)
	48 h EC_{50}=55 mg/L (nominal, under two hours UV-A irradiation)
Copepod [*Nitocra spinipes]*	96 h LC_{50}=92 mg/L(nominal)
Molluscs[*Crassostrea virginica*]:	144 h LC_{50} = 255 mg/L
	144 h EC_{50} = 28 mg/L (shell deposition, nominal)
Molluscs[*Littoina littorea*]:	96 h LC_{50} = 57 mg/L (nominal)
Algae[*Desmodesmus subspicatus*]:	72 h ErC_{50} > 500 mg/L (nominal, growth rate)
	72 h EbC_{50} = 575 mg/L (nominal, biomass)

The following chronic toxicity test results have been determined for aquatic species:

Fish [*Onchorynchus mykiss*]:	42 d LOEC = 0.05 mg/L(haemorrhage, measured)
Daphnid [*Daphnia magna*]:	21 d NOEC = 5 mg/L (reproduction and parent mortality, measured)
Molluscs[*Crassostrea virginica*]:	Significant growth inhibition at 0.05 mg/L (42 d, measured)
Algae[*Desmodesmus subspicatus*]:	72 h ErC_{10} = 240 mg/L (nominal; growth rate)
	72 h EbC_{10}= 28 mg/L (nominal; biomass)

Picric acid possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 10 and 100 mg/L for invertebrates, and chronic aquatic toxicity value below 0.05 mg/L for fish and invertebrates). However this chemical is considered to be not readily biodegradable and has a low bio-concentration potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

Total volume of production and import of picric acid was reported in the range of 100-1,000 tonnes in the fiscal years of 2006, 2007 and 2008 in Japan (sponsor country). However, picric acid is mainly imported in the sponsor country. Worldwide production volume of picric acid was not available.

Picric acid is used as synthetic raw material for a plant protective (chloropicrin) and dye or used as explosives in the sponsor country. Picric acid is also used as a desulfurization catalyser and a laboratory reagent in Japan. It is mentioned that picric acid is used as explosives, matches, in leather industry, electric batteries, etching copper, manufacture of coloured glass, textile mordant, also as reagent.

Picric acid may be released to waste water during the industrial use. A nation-wide environmental survey of chemicals conducted by the Japanese Ministry of Environment in fiscal year 1980 showed that picric acid was detected neither in environmental surface water nor in sediment in three different places in Japan. According to the Japanese PRTR (Pollution Release and Transfer Register) system, the emission volume of picric acid was reported to be less than 1 tonne in the fiscal years of 2006, 2007 and 2008 in the sponsor country. According to these results, the environmental exposure of picric acid seems to be insignificant in Japan.

Picric acid is known to be absorbed by all routes of exposure. It is also known that a solution of picric acid is irritating to eyes and to skin. A worker who handles picric acid or products containing picric acid should wear goggles, dust respirator, and protective gloves to minimize contact and intake. A Permissible Exposure Limit of 0.1 mg/m^3 (8 to 10 hour Time-Weighted Average) with skin designation and a short term exposure limit of 0.2-0.3 mg/m^3 are adopted in the USA, Australia, United Kingdom, and the Federal Republic of Germany.

Consumer exposure to picric acid may occur during the use of explosives, matches and electric batteries. However, the detailed information was not available.